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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,333	EINAT ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,20,21 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,20,21,40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 17, 20, 21, 40-43 are pending.

Applicant's traversal, the amendment to claims 17 and 20, and the addition of new claims 40-43 filed on 9/8/06 is acknowledged and considered by the examiner.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Provisional Application No. 60/056,453, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. No disclosure of RNA molecules that

target mRNA encoding a polypeptide having an amino acid sequence of SEQ ID NO: 10 could be located in the abovementioned provisional application.

The disclosure of the prior-filed applications, US Application No. 09/138,112 and 09/604,978, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. No disclosure of RNA molecules that target and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having an amino acid sequence of SEQ ID NO: 10, wherein the targeting results in mRNA degradation or disclosure for new claims 40-43 could be located in the above mentioned US applications.

The amendment filed on 3/17/04 provided new claims including new claims 17 and 20-21. Applicant cited pages 23, line 23, page 24, line 11 and page 26, line 11 for support of the new claims. Page 23, lines 23 is directed to a generic teaching of antisense and does not disclose support for an RNA molecule which targets mRNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10. Page 24, line 11 is directed to a journal articles teaching properties of antisense and does not disclose support for the new claims. Page 26, line 11 is directed to using ribozymes instead of antisense, but there is no support for the claims filed on 3/17/04.

The amendment filed on 9/8/06 does not have written support in the specification as filed. See 112 first paragraph new matter rejection.

Therefore, the effective filing date of instant claims 17, 20, 21, and 40-43 is considered to be the filing date of the amendment filed on 9/8/06.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the amendment filed on 3/17/04 introduced claims with, absence evidence to the contrary, no support under 112 first paragraph and the amendment was not filed on the filing date of the instant application (3/6/02).

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract is has more than 150 words. Correction is required. See MPEP § 608.01(b).

The status of the priority applications on page 1 needs updated.

Claim Objections

Claims 42 and 43 are objected to because of the following informalities: The phrase "An RNA molecule in accordance with claim" is an improper phrase for a dependent claims. Suggest replacing the term "An" on line 1 with the term -- The --. Appropriate correction is required.

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

If claim 20 is allowed it will have to be renumbered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 20, 21, 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter rejection:

The limitation 'An RNA molecule which targets and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10' in amended claim 17 and claims dependent therefrom and the limitation 'An RNA molecule consisting of a sequence that is the complement of at least seven nucleotides of target mRNA encoding a polypeptide consisting of the amino acid sequence of SEQ ID NO: 10 or an analogue thereof having at least 95% homology thereto, wherein said RNA molecule targets said target mRNA, resulting in prevention of processing, splicing, transport, or translation of the mRNA or in mRNA degradation' in new claim 40, 41, 43 and claims dependent therefrom is not supported by the instant specification. There appears to be no written description of the limitation in the application as filed. See MPEP § 2163.06. Applicant cites paragraph 0056 for amended claim 17 and paragraphs 0036 and 0058 for the limitation in claims 40-43. Paragraph 0036 discloses:

> The proteins may be produced recombinantly (see generally Marshak et al, 1996) and analogues may be due to post-translational processing. The term "analogue" as used herein is defined as a nucleic acid sequence or protein which has some differences in its amino acid/nucleotide sequences as compared to the native sequence of SEQ ID NOs:l-8 Ordinarily, the analogue will be generally at least 70% homologous over any portion that is functionally relevant. In more preferred embodiments the homology will be at least 80% and can approach 95% homology to the protein/nucleotide sequence.

Paragraph 0036 does not disclose SEQ ID NO: 10 or an RNA molecule that targets and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10. The paragraph is directed to a protein or DNA encoding proteins.

While it is acknowledged that the paragraph is directed to analogues of SEQ ID NOs: 1-8 (amino acid and DNA sequences) including 95% homology to the protein/nucleotide sequences. The paragraph is not directed to RNA molecules that would inhibit mRNA function and target an RNA encoding a polypeptide set forth in SEQ ID NO: 10. It appears that the paragraph is directed to functional proteins or DNA encoding a functional protein and not directed to RNA molecules with the desired biological activity (e.g., inhibiting gene expression). The skilled artisan understands that an antisense oligonucleotide does not encode a protein and an antisense oligonucleotide would have not an activity of the protein or DNA when expressed in cells.

Paragraph 0056 recites:

> Many reviews have covered the main aspects of antisense (AS) technology and its enormous therapeutic potential (Wright and Anazodo, 1995). There are reviews on the chemical (Crooke, 1995; Uhlmann et al, 1990), cellular (Wagner, 1994) and therapeutic (Hanania, et al, 1995; Scanlon et al, 1995; Gewirtz, 1993) aspects of this rapidly developing technology. Isolation of inhibitory antisense RNA is disclosed in Holzmayer (1992). Within a relatively short time, ample information has accumulated about the in vitro use of AS nucleotide sequences in cultured primary cells and cell lines as well as for in vivo administration of such nucleotide sequences for suppressing specific processes and changing body functions in a transient manner. Further, enough experience is now available in vitro and in vivo in animal models and human clinical trials to predict human efficacy.

Paragraph 0056 generically discloses antisense technology and does not disclose an RNA molecule that targets and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10.

Paragraph 0058 recites:

> The sequence target segment for the antisense oligonucleotide is selected such that the sequence exhibits suitable energy-related characteristics important for oligonucleotide duplex formation with their complementary templates, and shows a low potential for self-dimerization or self-complementation (Anazodo et al, 1996). For example, the computer program OLIGO (Primer Analysis Software, Version 3.4), can be used to determine antisense sequence melting temperature, free energy properties, and to estimate potential self-dimer formation and self-complementary properties. The program allows the determination of a qualitative estimation of these two parameters (potential self-dimer formation and self-complementary) and provides an indication of "no potential" or "some potential" or "essentially complete potential". Using this program target segments are generally selected that have estimates of no potential in these parameters. However, segments can be used that have "some potential" in one of the categories. A balance of the parameters is used in the selection as is known in the art. Further, the oligonucleotides are also selected as needed so that analogue substitution does not substantially affect function.

Paragraph 0058 generically discloses antisense technology and does not disclose an RNA molecule that targets and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10.

The limitations in the amended and new claims are not disclosed in the paragraphs cited by the applicant. Therefore, there is nothing in the specification that supports the new limitation as set forth in the instant claims.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

Claims 17, 20, 21, and 40-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17 and 21, as best understood, are readable on a genus of an RNA molecule that targets and is at least 95% homologous to mRNA consisting of RNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10, wherein the targeting results in mRNA degradation, wherein the genus of RNA molecules is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20 and 40-43, as best understood, are readable on a genus of an RNA molecule consisting of a sequence that is the complement of at least seven nucleotides of target mRNA encoding a polypeptide having the amino acid sequence of SEQ ID NO: 10, or an analogue thereof having at least 95% homology thereto, wherein said RNA molecule targets said target mRNA, resulting in prevention of processing, splicing, transport, or translation of the mRNA or in mRNA degradation, wherein the genus of RNA molecules is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification generically discloses prior art about antisense oligonucleotides (pages 24-27). The term "mRNA" in the instant claims indicates that the term reads on pre-mRNA (mRNA with introns) or processed mRNA (mRNA without introns or mature mRNA). The skilled artisan understands that pre-mRNA is subject to a number of maturation processes before the mature mRNA is translocated into the cytoplasm and transcribed. For example, the introns are cut out of the pre-mRNA and the 5' end of the mRNA is capped. The specification discloses SEQ ID NO: 10, which is the amino acid sequence for a human hypoxia-responding nucleic acid. The instant specification does not disclose a nucleotide sequence comprising the human hypoxia-responding gene. The prior art does not disclose the nucleotide sequence for the human hypoxia-responding gene. Agrawal et al. (2000-Molecular Medicine Today, Vol. 61, pp. 72-81) indicate, in particular regard to antisense methods of gene inhibition in cells of cells in vitro, that, "in

vitro, cellular uptake of antisense oligonucleotides depends on many factors including cell type, kinetics of uptake, tissue culture conditions and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide. It is therefore appropriate to study each antisense oligonucleotide in its own context and relevant cell line without generalizing the results for every oligonucleotide" (pg. 80, col. 1, 1st paragraph). While, one skilled in the art can envision a sequence that targets RNA encoding an amino acid sequence having the sequence of SEQ ID NO: 10 or seven nucleotides that target mRNA encoding a polypeptide consisting of SEQ ID NO: 10 or analogue thereof having at least 95% homology thereto, the skilled artisan would be unable to determine without further experimentation if the sequence had a function that was considered essential for the claimed genus of RNA molecules. As discussed above, there is a variation among species of the claimed genus of RNA molecules. Furthermore, the genus embraces RNA molecules that target to introns and cap structures that are neither disclosed in the specification nor the prior art. In addition, the skilled artisan understands that human hypoxia gene with polymorphisms are embraced by the claimed genus that are not disclosed in the instant specification or prior art. Furthermore, the specification does not disclose how to make a sufficient number of species to represent the genus of claimed RNA molecules. The specification does not make any RNA molecules embraced by the claimed genus. The only disclosure is paragraphs in the specification disclosing antisense technology. In addition, the claimed genus embraces RNA molecules that inhibit transcription by binding to human hypoxia-responding mRNA; however, transcription has already occurred if the mRNA is produced. Thus, the specification does not disclose how to make RNA molecules that bind to human hypoxia-responding mRNA and inhibit transcription.

The mere teaching in the specification of antisense is not sufficient to support the present claimed invention directed to a genus of RNA molecules with the desired biological activity. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of RNA molecules that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CAFC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of RNA molecules that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 9/8/06 have been fully considered but they are not persuasive.

In response that the amendment to claim 40 is very specific and does not include a large number of nucleotide sequences that are the complement of at least seven nucleotides of target mRNA encoding a polypeptide that is an analog of the sequence of SEQ ID NO: 10 having at least 95% homology thereto, the argument is not found persuasive because the RNA molecules read on a very large number of RNA molecules with varying structures. For example, the claims embrace cDNA, genomic DNA, pre-processed RNA or processed RNA. The specification does not disclose how to make a sufficient number of species to represent the claimed genus of RNA molecules. The art of record teaches that antisense molecules have to be determined experimentally (Gerwitz). In addition, Branch teaches, "internal structures of target RNAs and their association with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules (page 45). Gerwitz et al. (PNAS, 93:3161-3163, 1996) teach that mRNA targeting is to some extent a hit or miss process, accounting for many experiments in which the addition of an ODN yields no effect on expression (page 3161)." Uhlmann et al. teach, "It is clear from most in vitro studies that antisense oligonucleotides act most efficiently when directed against the initial part of the 5' non-coding region near the cap structure and against the region around the translation start codon (page 576)." (Chemical Review, 90: 544-84, 1990). Uhlmann et al. further teach, "Every mRNA has an individual secondary and tertiary structure that has a crucial influence on the efficiency of the target sequences" (page 576). "Although mRNA secondary structures can be calculated the efficiency of antisense oligonucleotides as inhibitors of protein translation has to be determined experimentally in practice" (page 576).

In response to applicant's argument that claims 42 and 43 do not encompass analogs and certainly should not be considered broader than the written description, the argument is not found persuasive for the reasons of record.

Response to Arguments

Applicant's arguments, see page 13, filed 9/8/06, with respect to 102(e) as being anticipated by Pavco have been fully considered and are persuasive. The rejection of claims 17-23 has been withdrawn because of the amendment to claim 17 and the cancellation of claims 18, 19 and 22-23.

Applicant's arguments, see page 13, filed 9/8/06, with respect to 102(e) as being anticipated by Monia have been fully considered and are persuasive. The rejection of claims 20 and 22 has been withdrawn because of the amendment to claim 17 and the cancellation of claim 22.

Applicant's arguments, see page 13, filed 9/8/06, with respect to 102(b) as being anticipated by Stinchcomb have been fully considered and are persuasive. The rejection of claims 20 and 22 has been withdrawn because of the amendment to claim 17 and the cancellation of claim 22.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

BRIAN WHITEMAN
PRIMARY EXAMINER